expression may be monitored using nucleic acid probes to the DNA or RNA equivalent of the of the gene transcript, and the quantification of gene expression levels, or alternatively, the final gene product itself (protein) can be monitored". Support for the amendment is also is found in the specification on page 60, line 23, wherein it is stated that: "BFA4 is upregulated in a large number of breast cancer tissues". Finally, further support for the amendment can be found on page 42, lines 19-22, wherein it is stated that: "The amino acid sequence used to determine sequence identity or similarity is that depicted in Figure 2. In another embodiment, the sequences are naturally occurring allelic variants of a protein having the sequence depicted in figure 2". No new matter is added.

Support for the amendments to claims 33 and 35 is found in original claim 1. No new matter is added.

Support for the amendments to claim 38 and newly added claim 39 is found in the specification on page 12, lines 29-31, and page 13, lines 1-3, wherein it is stated that: "A nucleic acid is a 'breast cancer nucleic acid' if the overall homology to the nucleic acid sequences of the figures is... as high as about 93 to 95 or 98%". No new matter is added.

The Objections to the Specification

Priority

The Examiner objected to the priority claim because neither the first sentence of the specification nor the Application Data Sheet (ADS) contain a specific reference to the prior applications for which the application is claiming the benefit of priority. The specification has been amended by inserting a paragraph that refers to the priority applications in the first sentence of the specification.

Specification

The disclosure was objected to because it contained an embedded hyperlink. The specification has now been amended to correct that oversight by

eliminating the hyperlink. Those paragraphs that contained the hyperlink were replaced with paragraphs that deleted the hyperlink. No new matter is added.

Title

The specification was also objected to because the Examiner alleged that the title was not descriptive of the elected invention. The title has now been amended to refer specifically to methods for detection and diagnosis of breast cancer. Reference to methods of screening for breast cancer modulators has been removed. No new matter is added.

The Rejections

Rejection Under 35 U.S.C. §112 First Paragraph

Enablement

Claims 32-38 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in such a way as to enable one skilled in the art to make and use the invention.

The Examiner agrees that the specification is enabling for methods of diagnosis in which increased expression is indicative of the presence of a breast cancer cell. However, the Examiner argues that because SEQ ID NO:1 is not up-regulated in some breast cancer tissue samples, and is expressed in a variety of other tissues, the specification does not enable one to detect the absence of a breast cancer cell.

The claims have been amended to recite that up-regulation of a nucleic acid encoding the BFA4 protein (SEQ ID NO:2) is indicative of the presence of a breast cancer cell. Because the specification enables any person to make and use the invention commensurate with the scope of the claims, the Applicants respectfully request that the rejection be withdrawn.

B. The Specification is Enabling for Sequence Variants Comprising SEQ ID NO:1.

The Examiner is concerned that the specification does not teach how to use all variants that are at least 75% identical with SEQ ID NO:1. The Examiner alleges that sequences at least 75% identical to SEQ ID NO:1 encompass many thousands of molecules differing from SEQ ID NO:1 in a variety of ways. The Examiner argues that the specification does not disclose that these other molecules are actually found in and/or are up-regulated in breast cancer. Therefore, the Examiner concludes that it is unpredictable as to whether up-regulation of all these possible molecules would be indicative of breast cancer, and therefore states that it would require undue experimentation to practice the methods of the invention with sequences other than SEQ ID NO:1.

To expedite the prosecution of the application, the claims have now been amended to recite "a nucleic acid encoding an amino acid sequence at least 95% identical to SEQ ID NO:2". Thus, the claims are now directed to the variation of the BFA4 protein that is expected to occur naturally within the entire human population. The methodology for detecting allelic variants of protein and nucleic acid molecules is well known in the art, and such methods are referred to for example, on page 12, lines 25-31, page 13 and page 14 of the specification.

To support her argument, that variants of SEQ ID NO:1 are not up-regulated in breast cancer, the Examiner cites Momeni *et al.* Momeni *et al.* investigated the role of the TRPS1 gene, which is 97.1% identical to SEQ ID NO:1 over its full length, as a cause of tricho-rhino-phalangeal syndrome type 1. The Examiner argues that because Momeni *et al.* are silent with respect to any relationship between TRPS1 and breast cancer, it is unpredictable whether variants of SEQ ID NO:1 are up-regulated in breast cancer.

As noted by the Examiner, the studies of Momeni *et al.* did not address the issue of breast cancer in patients with tricho-rhino-phalangeal syndrome type 1. Instead Momeni *et al.* were concerned with the underlying causes of tricho-rhino-phalangeal

syndrome type 1 itself. Although the studies did not provide any direct evidence relating to regulation of TRPS1 gene expression, Momeni *et al.* observed that that tricho-rhino-phalangeal syndrome type 1 is typically associated with mutations that result in *less* available TRPS1. Momeni *et al.* fail to show that TRPS1 is not up-regulated in individuals who have both tricho-rhino-phalangeal syndrome type 1and breast cancer. Therefore, the Examiner has not provided any evidence to support the allegation that variants of SEQ ID NO:1 are not up-regulated in breast cancer. Thus, the Examiner's rejection is improper and should be withdrawn.

The Examiner also cites studies by Chang *et al.* to support her allegation of non-enablement. Chang *et al.* cloned and studied the GC79 gene to determine its role in androgen-independent prostate cancer. Chang *et al.* did not ask whether or not GC79 was involved in breast cancer, therefore the fact that they are silent as to a role for GC79 in breast cancer is again, irrelevant to the issue of enablement. Furthermore, since GC79 is only 51.3% identical to the full length SEQ ID NO:1, it is outside the scope of the claims, both as filed and as amended. The enablement rejection is therefore improper and should be withdrawn.

C. Conclusion

The Applicants have identified a gene, BFA4, and shown that a high level of expression of the gene is statistically correlated with and breast cancer. Thus, determining the expression level of BFA4 is a useful tool for the detection of a breast cancer cell and the diagnosis of breast cancer. Therefore, the disclosure provided by the Applicants is sufficient, when combined with the teachings of the art, to permit one of skill to make and use the invention commensurate with the scope of the claims.

To maintain the enablement rejection, the subject matter cited as evidence by the Examiner must support the allegation that one skilled in the art, would not be able to make and use the claimed invention commensurate with the scope of the claims. In the

absence of evidence that sequences within the scope of the claims are not up-regulated in breast cancer, the rejection is improper and should be withdrawn.

Rejection Under 35 U.S.C. §112 Second Paragraph

Claims 32-38 are also rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter the Applicants regard as their invention. In particular, the Examiner has rejected claims 32-38 over the recitation of the language "detecting a nucleic acid... thereby determining the presence or absence of a breast cancer cell". The Examiner is unclear as to whether the presence of the nucleic acid indicates the presence or absence of a breast cancer cell.

Claim 32 has been amended to recite that "an increase in expression of the nucleic acid in the sample from the patient indicates the presence of a breast cancer cell in the patient". It should now be clear that increased expression of the nucleic acid indicates the presence of a breast cancer cell.

In addition, the defects in all the remaining claims are corrected by this amendment because all the remaining claims are either directly or indirectly dependent on claim 32.

Information Disclosure Statement

The Applicant has reviewed the corrections made by the Examiner to paper no. 7, the Information Disclosure Statement. The Applicants appreciate the Examiner's attention to detail, and thank the Examiner for her correction of the error.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Changes to the Specification

On page 9, lines 25-32 and page 10, lines 1-2 the following paragraph was substituted for the original paragraph:

In a preferred embodiment, breast cancer sequences are those that are up-regulated in breast cancer; that is, the expression of these genes is higher in carcinoma as compared to normal breast tissue. "Up-regulation as used herein means at least about a 50% increase, preferably a two-fold change, more preferably at least about a three fold change, with at least about five-fold or higher being preferred. All accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. GenBank is known in the art, see e.g., Benson, DA et al., Nucleic Acids Research 26:1-7 (1998) [and http://www.ncbi.nlm.nih.gov/]. In addition, these genes were found to be expressed in a limited amount or not at all in bladder, bone marrow, brain, colon, heart, kidney, liver, lung, muscle, pancreas, salivary gland, skin, small intestine, spinal cord, spleen,, stomach, thymus and uterus.

On page 13, lines 24-33 and page 14, lines 1-3 the following paragraph was substituted for the original paragraph:

Another example of a useful algorithm is the BLAST algorithm, described in Atschul et al., J. Mol. Biol. 215, 403-410 (1990) and Karlin et al., PNAS USA 90:5873-5787 (1993). A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Atschul et al., Methods in Enzymology, 266:460-480 (1996) [[http://blast.wustl/edu/blast/READ.html]]. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span =1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 parameters are dynamic values and are established by the

program itself depending upon the composition of the particular sequence and the composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. A % amino acid sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-BLAST-2 to maximize the alignment score are ignored).

Changes to the Claims

32. (Amended) A method for determining the presence or absence of a breast cancer cell in a patient, the method comprising:

(i) detecting a nucleic acid [comprising a] encoding an amino acid sequence at least [75] 90% identical to [SEQ ID NO:1] SEQ ID NO:2 in a sample from the patient, and

(ii) comparing expression levels of the nucleic acid in the sample from the patient to expression levels of the nucleic acid in a normal tissue sample,

[thereby determining the presence or absence of the] wherein an increase in expression of the nucleic acid in the sample from the patient indicates the presence of a breast cancer cell in the patient.

33. (Amended) The method of claim 32, wherein the sample from the patient comprises isolated nucleic acids.

34. (Amended) The method of claim 33, wherein the nucleic acids are mRNA.

35. (Amended) The method of claim 32, wherein the sample from the patient is breast tissue.

38. (Amended) The method of claim 32, wherein said detecting step is carried out by utilizing a biochip comprising a sequence at least [75] 90% identical to SEQ ID NO:1.

39. (New) The method of claim 32, wherein the nucleic acid is at least 95% identical to SEQ ID NO:1.